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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 09/462,993 | 04/17/2000 | MARIE-PAULE KIENY | 017753-122 | 5746 |

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| EXAMINER | |
|---|---|
| LI, QIAN J | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1632 | 16 |

DATE MAILED: 01/16/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/462,993 | KIENY ET AL. | |
| | Examiner | Art Unit | |
| | Janice Li | 1632 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *21-37 and 39-64* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *21-37 and 39-64* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *17 April 2000* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

## DETAILED ACTION

The amendment filed on November 5, 2001 has been entered as Paper #15. The examiner assigned to examine the application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Examiner Q. Janice Li, at Group Art Unit 1632.

Claims 21, 22, 24, 30, 39, and 40 have been amended, claims 41-64 are newly added. Claims 21-37, 39-64 are pending in the application and under current examination.

### *Claim Rejections - 35 USC § 112*

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

ENABLEMENT REQUIREMENT

The prior rejection of claims 21-37, 39 and 40 stands for the reasons advanced on pages 3-7 of the prior Office action (paper No. 13), and applies to the newly amended claims 41-64. The rejection and response to the Remark will be given or reiterated as following.

Claims 21-37 and 39-46 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for reducing tumor cell load in mice by administering a recombinant vector expressing E6 and E7 polypeptide of a HPV-16

linked with a particular membrane anchoring sequence, does not reasonably provide enablement for reducing tumor cell load in humans, or linking with any membrane anchoring sequence. In addition, the specification does not reasonably provide enablement for reducing tumor cell load in mice or in humans by administering a recombinant vector expressing any immunogenic polypeptide linked with any membrane anchoring sequence. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The applicants argue in Paper #15 that "*claims 21-37 are directed to compositions, and as such, only one valid use need be disclosed and enabled for the claimed compositions to satisfy the requirements of first paragraph of 35 U.S.C. 112*". The argument has been carefully considered but found not persuasive.

With respect to claim breadth, the standard under 35 U.S.C. §112, first paragraph, entails the determination of what the claims recite and what the claims mean as a whole. "WHEN A COMPOUND OR COMPOSITION CLAIM IS LIMITED BY A PARTICULAR USE, ENABLEMENT OF THAT CLAIM SHOULD BE EVALUATED BASED ON THAT USE". (MPEP 2164.01c) When analyzing the enabled scope of the claims, the intended use is to be taken into account because the claims are to be given their broadest reasonable interpretation that is consistent with the specification. "An antitumoral composition" is defined as a composition for therapeutic use, to prevent, alleviate, treat, or cure a tumor within the animal to which the substance is administered, therefore, will be evaluated by the standard.

The applicants argue in Paper #15 that "*the Examiner has presented no substantive evidence beyond the Examiner's personal speculation, to support the implied assertion that the presently claimed methods may not be used by one of skill in the art to provide a prophylactic benefit*". The argument has been carefully considered but found not persuasive.

In response, it is noted that the applicants overlooked the citation in page 5, lines 2-15 of Paper # 13, which clearly indicates that the Examiner's view on the subject matter is fully supported by the teaching of the skilled artisan (see page 5, the citation from *McCluskie et al*). In addition, in order to particularly point out the barriers in cancer vaccination, the applicants' attention is directed to the teachings of *Bodey et al,* and *Radoja et al*, which teach that although the mouse model has served as a useful tool for study cancer therapy, the artificially established tumor differs from the naturally occurring cancer in humans. *Bodey et al* (Anticancer Res 2000;20:2665-76) review cancer vaccines in cancer immunotherapy, "THE THEORETICAL BASIS FOR ALL OF THESE APPROACHES IS VERY WELL FOUNDED. ANIMAL MODELS, ALBEIT HIGHLY ARTIFICIAL, HAVE YIELDED PROMISING RESULTS. CLINICAL TRIALS IN HUMANS, HOWEVER, HAVE BEEN SOMEWHAT DISAPPOINTING...", "THE CANCER VACCINE APPROACH TO THERAPY IS BASED ON THE NOTION THAT THE IMMUNE SYSTEM COULD POSSIBLY MOUNT A REJECTION STRENGTH RESPONSE AGAINST THE NEOPLASTICALLY TRANSFORMED CELL CONGLOMERATE. HOWEVER, DUE TO THE LOW IMMUNOGENICITY OF TUMOR ASSOCIATED ANTIGENS, DOWNREGULATION OF MHC MOLECULES, THE LACK OF ADEQUATE COSTIMULATORY MOLECULE EXPRESSION, SECRETION OF IMMUNE INHIBITORY CYTOKINES, ETC., SUCH EXPECTATION ARE RARELY FULFILLED... FAULTY ANTIGEN PRESENTATION WHICH COULD RESULT IN TOLERANCE INDUCTION TO THE ANTIGENS CONTAINED WITHIN THE VACCINE,

AND SUBSEQUENT RAPID TUMOR PROGRESSION." (page 2665, column one). *Radoja et al* (Mol Med 2000;6:465-79) teach that cancer-induced defective cytotoxic T lymphocyte is probably another mechanism how tumor antigen escape immune surveillance. "THE NOTION THAT A DEFICIT IN IMMUNE CELL FUNCTIONS PERMITS TUMOR GROWTH HAS RECEIVED EXPERIMENTAL SUPPORT WITH THE DISCOVERY OF SEVERAL DIFFERENT BIOCHEMICAL DEFECTS IN T LYMPHOCYTES THAT INFILTRATE CANCERS" (abstract). "ACCUMULATION OF CIRCULATING ANTITUMOR IMMUNOGLOBULIN G IN CANCER PATIENTS SHOW THAT THE PRIMING PHASE OF ANTITUMOR IMMUNE RESPONSE IS FUNCTIONAL DURING THE RELATIVELY SLOW PROCESS OF NASCENT TUMOR GROWTH...IN BOTH HUMAN CANCER PATIENTS AND RODENTS BEARING TUMORS OF DIFFERENT HISTOLOGIC ORIGIN, SYSTEMIC IMMUNITY IS NOT PROFOUNDLY SUPPRESSED..." "HOWEVER, INHIBITION OF A SPECIFIC ANTITUMOR IMMUNE RESPONSE HAS BEEN OBSERVED FREQUENTLY. A VARIETY OF MECHANISM HAVE BEEN PROPOSED TO ACCOUNT FOR DEFECTIVE ANTITUMOR IMMUNE RESPONSE, INCLUDING: SECRETION OF SUPPRESSIVE FACTORS IN THE TUMOR MICROENVIRONMENT, THE LACK OF EXPRESSION OF COSTIMULATORY SIGNALS ON TUMOR CELLS, INDUCTION OF REGULATORY T CELLS HAVING A SUPPRESSIVE PHENOTYPE, LOSS OF ANTIGEN PRESENTATION FUNCTION IN THE TUMOR, LOSS OF EXPRESSION OF HLA CLASS I ANTIGEN PRESENTING MOLECULES IN TUMORS, TUMOR-INDUCED T-CELL SIGNALING DEFECTS, LOSS OF TUMOR ANTIGEN EXPRESSION, IMMUNOLOGICAL IGNORANCE AND, SINCE MANY TUMOR ANTIGENS ARE EITHER UNMODIFIED SELF OR EPITOPES CLOSELY RELATED TO SELF, THE REDUCTION OF THE REPERTOIRE OF POTENTIAL HIGH AFFINITY ANTITUMOR T-CELL CLONES DURING T-CELL MATURATION IN THE THYMUS" (Introduction). Thus, it is evident that at the time of the invention, the skilled artisan in the relevant art, while acknowledging the significant potential of immunotherapy for cancer, still recognized that such therapy was neither routine nor accepted, and awaited significant development and guidance for its practice. Therefore, it is incumbent upon applicants to

provide sufficient and enabling teachings within the specification for such therapeutic regimen. Although the instant specification provides ex vivo and in vivo data in a mouse tumor model to illustrate a potential therapeutic use of the claimed compositions and methods, it is not enabled for its full scope because the art-recognized barriers in achieving successful cancer immunotherapy and differences in immune responses between a mouse tumor model and cancer patients.

With regard to the broadly claimed immunogenic polypeptide as part of an antitumoral composition, the term "immunogenic polypeptide" encompasses any graft antigen, any pathogen, any allergen and other foreign polypeptides which are not known to be associated with a tumor, the mechanism of antitumor effects from such polypeptide has not been taught by the specification, thus, the skilled artisan could not practice the claimed invention without undue experimentation.

Furthermore, even limiting the recited immunogenic polypeptides to a tumor-associated antigen, or to a polypeptide derived from papilomavirus, the claimed invention would still have failed to meet the enablement requirement. This is because the unpredictability of the art of cancer immunotherapy, the levels of the skilled in the art, and the guidance provided in the specification. As taught by *Boedy et al* and *Radoja et al*, the success or failure of cancer immunotherapy is determined by many distinct factors both from the nature of the antigen itself and the host immune responses. The etiology and the mechanism leading to a given cancer differs significantly among different cancer types. As of the post-filing date of the cited publications, failure far exceeds success in view of tumor immunotherapy as a whole. Thus, it is incumbent

upon applicants to provide sufficient and enabling disclosure within the specification to guide the practice of the invention as it is broadly claimed. However, the teachings of instant specification are limited to E6 or E7 polypeptides of HPV-16, a particular papilomavirus, which is only one species of a potentially uncountable numbers of tumor antigens as a genus. It is noted that in applications directed to inventions in arts where the results are unpredictable, the disclosure of a single species usually does not provide an adequate basis to support generic claims. In re Soll, 97 F.2d 623, 38 USPQ 189 (CCPA 1938). In cases involving unpredictable factors, such as most chemical reactions and physiological activity, more may be required. In re Fisher, 166 USPQ 18 (CCPA 1970). See also In re Wright, 999 F.2d 1557, 27 USPQ2d 1510 (Fed. Cir. 1993); In re Vaeck, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). This is because it is not obvious from the disclosure of one species, whether other species will work. In re Dreshfield, 110 F.2d 235, 45 USPQ 36 (CCPA 1940), gives this general rule: "IT IS WELL SETTLED THAT IN CASES INVOLVING CHEMICALS AND CHEMICAL COMPOUNDS, WHICH DIFFER RADICALLY IN THEIR PROPERTIES IT MUST APPEAR IN AN APPLICANT'S SPECIFICATION EITHER BY THE ENUMERATION OF A SUFFICIENT NUMBER OF THE MEMBERS OF A GROUP OR BY OTHER APPROPRIATE LANGUAGE, THAT THE CHEMICALS OR CHEMICAL COMBINATIONS INCLUDED IN THE CLAIMS ARE CAPABLE OF ACCOMPLISHING THE DESIRED RESULT." It is highly unpredictable whether the deficiency in cancer immunotherapy as aforementioned would be overcome by linking a membrane anchoring sequence to any or most of a given tumor antigen. Accordingly, in view of the quantity of experimentation necessary to determine the antitumor effect for any given tumor antigen apart from E6 and E7 polypeptides, the lack of direction or guidance provided by the specification with regard to the breadth of the claims directed

to the use of numerous therapeutic polypeptide compositions, it would have required undue experimentation for one skilled in the art to make and/or use the claimed invention as they are broadly claimed.

For the reasons of record and those set forth above, the instant specification fails to meet the enablement requirement.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 21-37, 39-64 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 21 and 44 are vague and indefinite because the claim recitation "[said polypeptide] is modified by inserting a membrane anchoring sequence". It is unclear which part of the polypeptide the membrane anchoring sequence is inserted to and if such insertion would cause changing of immunogenicity.

Claim 21 and 44 are vague and indefinite because of the claim recitation "a membrane anchoring sequence", because "membrane" encompasses cellular membrane and intracellular membrane, it is unclear which membrane the claims embrace.

***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The rejection of claims 21, 22, 24-26, 34-37, 39 and 40 under 35 U.S.C. 102(b) as being anticipated by *Lin et al* is withdrawn in view of the argument and exhibition F, to show that LAMP-1 protein is located in the lysosomal/endosomal membrane, but not cellular membrane.

New grounds of rejections are necessitated upon further search of databases.

Claim 21-23, 35-37, and 41 are rejected under 35 U.S.C. 102(b) as being anticipated by *Arnold et al* (Virol 1994;198:703-08).

These claims are drawn to a composition comprising at least one recombinant vector comprising sequences encoding immunogenic polypeptide having a naturally nonmembrane location and modified by incorporating a membrane anchoring sequence so as to have a membrane location at the surface of the cells in which it is expressed, wherein said polypeptide naturally has a nuclear location, wherein said membrane anchoring sequence is HIV virus env glycoprotein, wherein the composition is suitable to inject to animals.

*Arnold et al* teach a recombinant DNA plasmid comprising an immunogenic polypeptide (HRV14), and the HIV transmembrane envelop glycoprotein, gp41 (left column 1st paragraph, page 705). A viral polypeptide naturally has a nuclear location. *Arnold et al* go on to teach that the composition is administered to rabbits and ferrets to produce antibodies (right column, page 706) and such chimeric HRVs could be used to optimize an immune response via making the foreign immunogen more stimulatory, perhaps by making it extend further out on the surface of the virus. Thus, *Arnold et al* anticipate these claims.

The claim recitation "an antitumoral composition" has not been given patentable weight in the instant rejection because the intended use for tumor immune therapy does little toward defining structure of the claimed composition. Rather, the structure of the polynucleotide and polypeptide sequences are relied upon for structural determination.

Claims 21 and 36 are rejected under 35 U.S.C. 102(b) as being anticipated by *Geogiou et al* (US 5,348,867).

Claims 21 and 36 are drawn to a composition comprising at least one recombinant vector comprising sequences encoding immunogenic polypeptide having a naturally nonmembrane location and modified by incorporating a membrane anchoring sequence so as to have a membrane location at the surface of the cells in which it is expressed.

*Geogiou et al* teach a versatile recombinant vector that will promote transport of a periplasmic or other protein to the external surface of the outer membrane of a gram-negative bacterial cell. The said vector comprising a membrane targeting sequence, a membrane translocation sequence, and a gene segment encoding any of a variety of

proteins (column 3, lines 42-52). They go on to teach such proteins could be immunogenic polypeptides (column 7, line 17), and the vector could be used to produce immunogenic polypeptides and vaccination. Thus, *Geogiou et al* anticipate the claims.

Claim 21 and 36 are rejected under 35 U.S.C. 102(e) as being anticipated by *Stahl et al* (US 5,958,736).

*Stahl et al* teach a recombinant DNA comprising an immunogenic polypeptide, and a membrane anchoring sequence (abstract). *Stahl et al* go on to teach that the delivery vectors including vaccinia virus and other viral vectors (column 1, lines 24-40). Thus, *Stahl et al* anticipate these claims.

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The prior rejection of claims 21, 22, 24-27, 34-37, 39 and 40 under 35 U.S.C. 103(a) as being unpatentable over *Lin et al* in view of *Boursmell et al* is withdrawn due to the withdrawal of the 102 (b) rejection as anticipated by *Lin et al.*

The prior rejection of claims 21, 24, 28 and 29 under 35 U.S.C. 103(a) as being unpatentable over *Lin et al* in view of *Jarrett et al* is withdrawn due to the withdrawal of the 102 (b) rejection as anticipated by *Lin et al.*

The prior rejection of claims 21, and 31-33 under 35 U.S.C. 103(a) as being unpatentable over *Lin et al* in view of *Chow et al, He et al,* and *kim et al* is withdrawn due to the withdrawal of the 102 (b) rejection as anticipated by *Lin et al.*.

***Conclusion***

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Q. Janice Li whose telephone number is 703-308-7942. The examiner can normally be reached on 8:30 am - 5 p.m., Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah J. Clark can be reached on 703-305-4051. The fax numbers for the organization where this application or proceeding is assigned are 703872-9306 for regular communications and 703-872-9307 for After Final communications.

Any inquiry of formal matters can be directed to the patent analyst, Kay Pinkney, whose telephone number is (703) 305-3553.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-1235. The faxing of such papers must conform to the notice published in the Official Gazette 1096 OG 30 (November 15, 1989).

Q. Janice Li
Examiner
Art Unit 1632

QJL
January 14, 2002

JAMES KETTER
PRIMARY EXAMINER